REMARKS

Amendments to the Claims

Claim 1 has been amended. Support for the Amendment to claim 1 is found in the Specification at page 3, last paragraph.

Claims 18, 19, and 21 have been amended. Support for the Amendment to claims 18, 19, and 21 is found in the Specification at page 3, last paragraph.

New claim 22 has been added. Support for claim 22 is found in the Specification on page 13, lines 18-23.

New claims 23-26 have been added. Support for claims 23-26 is found in the Specification on page 3, lines 34-37.

No new matter has been added.

Interview Summary

Applicants thank the Examiner for speaking with their representative on January 8, 2009. During the Interview Applicants' representative discussed the anticipation and obviousness rejections with the Examiner Xie and Examiner Spector.

35 U.S.C. §102(b)

The Examiner rejects claims 17 and 20 under 35 U.S.C. § 102(b) as anticipated by Fong et al. Applicants respectfully traverse and request reconsideration and withdrawal of the rejection.

The Examiner appears to believe that Fong teaches that DCs can be stimulated by one or more stimuli based on Figure 2 of Fong. However Applicants submit that Figure 2 of Fong relates specifically to the *in vivo* processes of DCs (e.g., the figure is titled "DC life cycle") and not to any particular DC treatment. In contrast, Table 3, to which the Examiner also refers, relates to

aspects of treatment without mentioning a specific stimulation. Applicants submit that the combination of these two disparate concepts is pure hindsight on the part of the Examiner. Moreover, the specific combination of LPS and IFN-γ is neither explicitly mentioned or made obvious in Figure 2 of Fong.

Thus, Applicants submit that Fong hypothesizes that in vivo stimulation of DCs *might* require an "independent danger signal" (Fong 251, line 1), but does not hypothesize that more than one "danger signal" can be used, that this stimulation could possibly be *ex vivo*, or that the combination of LPS and IFN- γ would be useful for stimulating DCs incubated in the presence of tumor-specific antigens. Thus, Applicants submit that Fong clearly does not anticipate the present invention.

35 U.S.C. §103

The Examiner rejects claims 1, 3-5, 9, 18, 19, and 21 under 35 U.S.C. §103 as unpatentable over Fong in view of Lapointe.

The Examiner states that while Fong does not teach *ex vivo* stimulation with LPS and IFN-γ, Lapointe suggests that "[o]ptimizing DC activation, by stimulating with multiple agents, may improve current efforts towards the generation of potent T cell responses *in vivo*." (Lapointe, page 3296, col. 2).

Fong in combination with Lapointe does not teach each element of the claims.

Applicants submit that Fong in combination with Lapointe does not teach each element of the claims. Specifically, Fong does not teach stimulation with LPS and IFN- γ and Lapointe does not remedy this deficiency. Lapointe only teaches exposure to both IFN-γ and LPS for a period of 24 hours. Lapointe does not teach that exposure should be limited to a period from 1-10 hours. Lapointe also does not differentiate between active DCs and exhausted DCs. Thus, Applicants submit that the combination of Fong and Lapointe does not establish a *prima facie* case of obviousness.

Lapointe teaches away from the present invention.

Applicants also submit that Lapointe teaches away from the present invention because it specifically indicates that IL-12 production is optimum after 24 hours. Lapointe teaches that DC are stimulated for 6, 12, or 48 hours with the CD40Ls and LPS. (Lapointe, Fig. 1, C). But synergistic IL-12 production is only achieved at 24 and 48 hours. *Id.* In contrast, the present invention requires that the cells are exposed to IFN-γ and LPS for a period of 1-10 hours, after which the cells are administered or frozen. The Specification teaches that this time period is important to maximize IL-12 release, and that after 48 hours the DCs are exhausted. (Specification, page 3, lines 34-35 and page 8, first paragraph).

Thus, following the teachings of Lapointe would suggest that the cells are exhausted DCs and not suitable for the intended use of the present invention.

Therefore, Applicants submit that because Lapointe teaches away from the present invention the combination of Fong and Lapointe do not render the present invention obvious. Applicants request that the rejection be withdrawn.

Neither Fong or Lapointe address the toxicity of LPS

Applicants submit that prior to the present invention, one of skill in the art would not have administered LPS to a human patient as part of a cancer therapy because LPS is a toxin. More importantly, LPS is the central toxin which causes septic or enterotoxin shock in humans. As discussed in the Declaration by Dr. Felzmann submitted with the Amendment of June 10, 2008, LPS would not have been used by one of skill in the art at the time of filing due to its toxic effects. Thus, Applicants submit that the present invention would not have been obvious to one of skill in the art at the time of filing. Applicants request that the rejection be withdrawn.

Unexpected Results

Applicants submit and the Examiner agreed during the interview to take into consideration that the exposure of the DCs to IFN-γ and LPS for a period of 2 hours shows active DCs which have a therapeutic effect compared to a 24 hour exposure which shows exhausted DCs. The Specification distinguishes "active DCs" which produce IL-12 from "exhausted DCs" which "do not produce IL-12 any more." (Specification, page 4, lines 5-6). In order to capitalize on the IL-12 the Specification states that:

> It is, however, important to deliver the DCs according to the present invention in a state, where IL-12 release still takes place, i.e. immediately after the preparation of the tumor- or pathogen-specific IL-12 releasing DCs or at least within 10, especially within 2-6 hours thereafter, ideally about 2 hours after completion of the preparation.

(Specification, page 3, lines 32-37).

Tumor-specific therapeutic effectiveness is shown at page 16, line 30 and Figure 9. Mouse DCs were loaded with either NPT-protein from lysed NPT+ cancer cells, recombinant NPT-protein, or NPT peptide fragments (nonameric peptides). The DCs were then stimulated with IFN-γ and LPS for a period of either 2 hours or 24 hours and injected into mice. The mice were subsequently injected with the NPT+ tumor cell line.

Figure 9 shows that in mice which were given the NPT+ cancer cell line, and which had active DCs, 3/5, 4/5, or 5/5 mice were tumor free depending on whether they were given NPT from lysed cells, recombinant NPT, or NPT peptide fragments. In contrast, only one mouse was tumor free in any of the mice treated with exhausted DCs. Applicants submit that these results are unexpected in view of the teachings of Lapointe and Fong, especially since Lapointe suggests that 48 hours of stimulation is better than a shorter period of time.

Further evidence of unexpected results is shown by the results of the human phase I clinical trial discussed in the Specification. (page 22, beginning at line 16). The Specification suggests that because the patients all had a history of advanced disease and of extensive chemo- or radio-

therapy, thus there was no expectation of tumor regression. However, "several of the patients had stable disease for a prolonged period of time." (Specification, page 22, lines 19-20).

Moreover, these unexpected results are not limited to the 2 hour exposure time. The Specification teaches that the critical time point is 2-10 hours after the preparation has been completed, preferably "within 2-6 hours" after the preparation has been completed, i.e. after the LPS and IFNγ has been added. As shown by Felzmann et al., "Semi-mature IL-12 secreting dendritic cells present exogenous antigen to trigger cytolytic immune responses," Cancer Immunol. Immmunother. (2005) 54:769-780, cells incubated for 6 hours with LPS and IFN-γ and subsequently rinsed had "sustained release" of IL-12, whereas DCs which were exposed to LPS and IFN-γ for 48 h no longer secreted IL-12 when cultured in fresh medium. (Felzmann, 2005, page 772, lines 35-41 and Figure 1(c)). Applicants herein provide a Declaration under 37 C.F.R. § 1.132 from Dr. Felzmann in order to submit in Declaration form the experimental results reprinted in Felzmann (2005). Accordingly, Applicants submit that the unexpected results are shown with 6 hour exposure as well. This six hour time point supports the assertion in the Specification for a period of 1-10 hours as described at page 3, lines 32-37. It is reasonable to expect that the 10 hour time point would show the same results as the six hour time point, especially considering the extreme of the prior art 24-48 hour time points. Applicants request that the Examiner reconsider and withdraw the obviousness rejection in view of the unexpected results.

CONCLUSION

In view of the above remarks, Applicants request the Examiner withdraw all rejections.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson Reg. No. 30,330 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: February 13, 2009

Respectfully submitted,

By _____

Attached: Felzmann Declaration

Leonard R. Svensson
Registration No.: 30,330
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive
Suite 260
San Diego, California 92130
(858) 792-8855
Attorney for Applicant